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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/968,800	11/22/97	DRMANAC	R 20411720

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EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1646	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/968,800	DRMANAC et al
Examiner	**Group Art Unit**
Fozia Hamud	1646

☒ Responsive to communication(s) filed on *Apr 5, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-9* is/are pending in the application.

Of the above, claim(s) *4-9* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-3, in Paper No 10 on (April 5, 1999) is acknowledged.

Claims 4-9 are withdrawn from consideration by the Examiner as they are drawn to non-elected groups.

Oath

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. 120 which discloses and claims subject matter in addition to that disclosed in the prior copending applications (serial No: 08/820,619, 08/876,993 copending), acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing dates of the continuation-in-part applications.

Specification

3a. The title of the invention is not descriptive and the word "novel" is not considered as part of the title of an invention and the Patent and Trademark Office does not include such words at the beginning of the invention. A new title is required that is clearly indicative of the invention to which the claims are directed without the word "novel". The following title is suggested "Polynucleotide encoding EGF-receptor like protein obtained from a cDNA library of fetal liver-spleen....."

3b. It is noted that this application appears to claim subject matter disclosed in prior copending Applications, however, it does not list the entire serial numbers for two of these prior applications. The serial numbers for all of the prior applications must be listed as the first sentence of the specification of this application if applicant intends to rely on the filing dates of these prior applications under 35 U.S.C. 119(e) or 120. See 37 CAR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Claim objections

4. Claim 1 is objected to because of the following informalities:

Claim 1 is objected to as using improper/incomplete Markush language. (See M.P.E.P. 2173.05(h).) Applicants should use "and" as an alternative embodiment between SEQ ID No.1 and SEQ ID No 2. .

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

5a. Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-3 recite "a polynucleotide comprising...." which encompasses the polynucleotide as it occurs in nature. However, since Applicants do not intend to claim a naturally occurring product amendment of the claims to show the hand of man would obviate this rejection. It is suggested that the claims be amended to recite " an isolated and purified polynucleotide comprising .....".

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 2 of the instant invention are directed to a polynucleotide encoding a protein which contains an EGF motif that is similar to the EGF motif of the drosophila *Notch,* the EGF motif of CD97 and the EGF consensus motif, (page 38, lines 15-24). The specification describes the polynucleotide of SEQ ID NO: 1 as being an EST for a family member of the EGF-containing genes with most similarity to the EGF motifs of drosophila *Notch* and CD97 with 32% and 38% homology respectively, (page 38, lines 18-20).

Claims 1 and 3 are drawn to a polynucleotide of SEQ ID No: 2 encoding a polypeptide which is also similar in protein sequence to the EGF motifs of drosophila *Notch* and CD97 with 31% and 34% homology respectively. The protein encoded by the polynucleotide of SEQ ID No: 2 is thought to be a member of the EGF-repeat containing family because it shares the highly conserved characteristic spacing of cysteines and glycines which define EGF motifs (page 38, lines 25-29).

One stated use of the polynculeotides of the present invention is for producing the encoded protein recombinantly (see page 36, lines 23-30). The specification discloses that EGF and other ligands for EGF receptor (which the protein encoded by the instant polynucleotides share similarities with) have been implicated in various cancers and may be useful as therapeutic agents, (page 39, lines 13-15). However, the protein encoded by the instant polypeptides have never been expressed and no biological activity of the protein was assayed or determined. Furthermore, one of ordinary skill in the art would not reasonably expect a protein which only has 24-38% identity to another protein to possess the same activity with any degree of predictability. This would equate to mutation of a protein such that it is only 24-38% identical to the native protein and still hope that it would retain the function of the native protein. The specification provides no working examples as to the activity of the protein encoded by the claimed polynucleotides, and one of ordinary skill in the art would not be able to predict what activity would be possessed by the protein of the instant application based solely because it contains EGF-like repeats similar to the EGF-repeat containing family of proteins. The specification has not provided guidance as to how many EGF-like repeats these proteins contain? and how many of those are necessary for biological activities. It is well known in the art that a wide variety of proteins with unrelated functions contain EGF-like domains that share

the characteristic spacing of cysteines and glycines. For example, the coagulation factors I X and X contain two tandemly arranged EGF-like domains, (Selander et al, page 8111, first paragraph), E-selectin a cytokine-inducible, endothelial-cell-specific membrane glycoprotein that mediates the adhesion of neutrophils also contains an EGF-like domain which is necessary for neutrophil adhesion, (Graves et al, page 532). The fact that the protein encoded by the polynucleotides of the instant Application shares 24-38% identity with the EGF-like domain containing family of proteins is not enough information about this protein. How many EGF-like repeats does it have? How many of those are necessary for structural and functional integrity? And what is the exact role of this protein, is it involved in blood coagulation, neural development or cell adhesion ? Since the EGF-like domain containing proteins are diverse with different physical characteristics and biological activities, one of ordinary skill in the art would not be able to predict the activity and physical characteristics of a protein by the mere knowledge that it contains EGF-like domains. Furthermore, the presence of "conserved" amino acid residues is not predictive of what biological activity will be retained by that protein.

An example of structurally related proteins which have divergent function are platelet-derived growth factor (PDGF) and vascular endothelial cell growth factor (VEGF) (U.S.S.N. 5,194,596). These two proteins have a great deal of sequence similarity, implying that they are proteins from a structurally-related "family". If structure related directly with function, one of ordinary skill in the art would expect that the two proteins could be used in a similar manner. However, this is not the case. PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells. Conversely, VEGF is mitogenic for vascular endothelial cells but not for vascular smooth muscle

cells. (See U.S.S.N. 5,194,596, column 2, line 46 through column 3, line 2.) These very related proteins have a specificity which is exactly opposite one another and which could not be predicted based on a similarity in their amino acid sequences.

In terms of amino acid sequence homology, a single mutation in a protein is capable of altering biological activity and it is not predictable which amino acids are necessary for activity without first testing and determining those amino acids which are required for biological activity. Examiner has cited Cunningham et al. who teaches that in a strategy called alanine-scanning mutagenesis, replacement of a cluster of amino acids with alanine in human growth hormone (hGH), resulted in more than four times lower binding affinity to the hGH receptor (see page 1081, abstract, lines 1-8). Alanine was chosen as the replacement residue because alanine eliminates the side chain beyond the carbon, yet does not alter the main-chain conformation (as can glycine or proline) nor does it impose extreme electrostatic or steric effects (page 1081, column 1, lines 18-23), and in general, alanine is the most abundant amino acid frequently found in both buried and exposed positions in proteins (page 1081, column 1, lines 24-27). However, as disclosed by Cunningham, single substitutions by alanine in 42 out of the 65 hGH mutants resulted in tertiary structure changes reflected by changes in binding affinity of the mutants to the receptor, because side chains of amino acids are important for modulating binding of ligands to receptors (page 1081, column 1, lines 14-17; page 1081, Figure 1 and page 1082, Table 1).

Should Applicant establish that the proteins encoded by SEQ ID Nos: 1 and 2 possess activities similar to EGF-repeat containing family of proteins (as implied by the specification), the instant specification would still fail to adequately describe and enable the administration of the

proteins for any medical condition (blood clotting problems? inflammation? cancer?) and no other patentable uses are set forth for the DNA encoding the protein.

In summary, the amount of experimentation required for one of ordinary skill in the art to use the claimed invention, polynucleotides encoding novel EGF receptor like protein, would be undue. In Ex parte Forman, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986), the Board considered the issue of enablement in molecular biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. The level of skill in the art of molecular biology is high, but the nature of the invention is not well characterized (i.e. the polynucleotide encoding EGF-receptor like protein of the instant invention is novel). Therefore, the state of the prior art is relatively silent to the invention that is claimed. Although working examples are not required, they are one of the factors that must be considered when determining enablement, especially in light of the lack of guidance in the specification and the nature of the invention; in the instant case, there are no working examples or assays for determining activity (since no activity has been disclosed).

Conclusion

No claim is allowed.

The claims are free of the prior art of record.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Group1646
May 7, 1999

PREMA MERTZ
PRIMARY EXAMINER